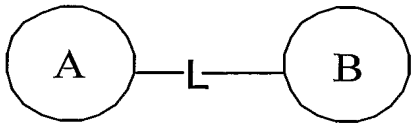
CLAIMS

1. An agent for treating a pulmonary disorder represented by the structure:



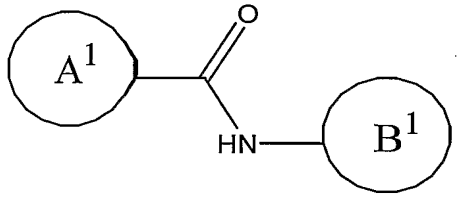
wherein

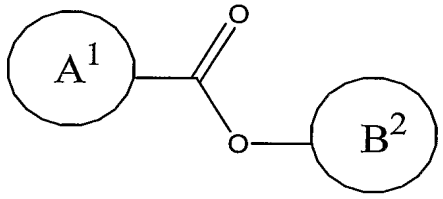
A is a mast-cell stabilizer;

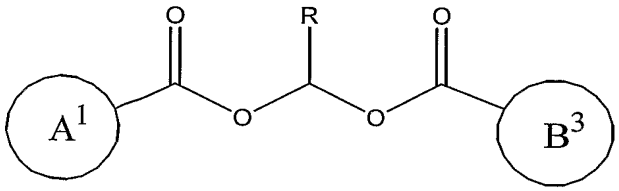
L is a covalent linkage;

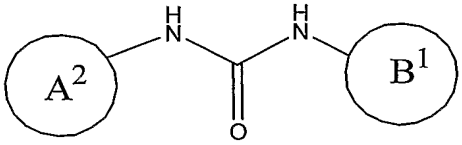
B is an iNOS inhibitor.

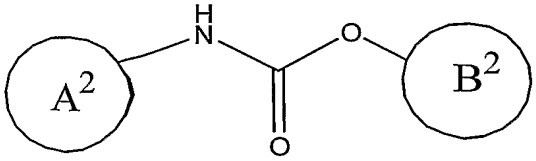
2. An agent according to claim 1 wherein L is chosen from –CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and –(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:

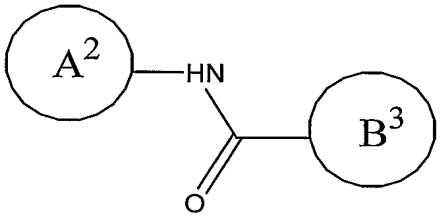


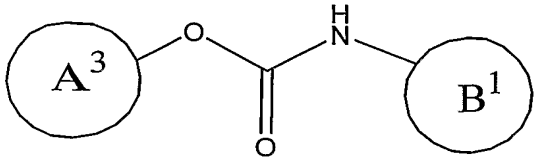


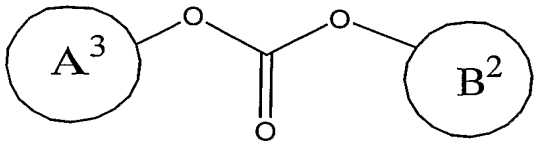


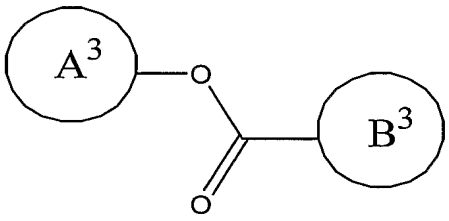












and

wherein

A^1 is a mast-cell stabilizer having a carboxylic acid substituent;

A^2 is a mast-cell stabilizer having an amine substituent;

A^3 is a mast-cell stabilizer having an alcohol substituent;

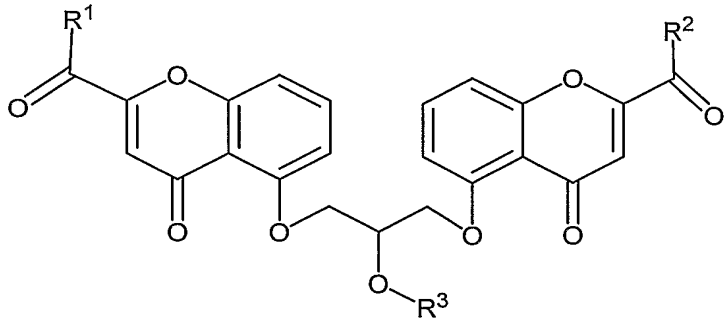
B^1 is an iNOS inhibitor having an amine substituent;

B^2 is an iNOS inhibitor having an alcohol substituent;

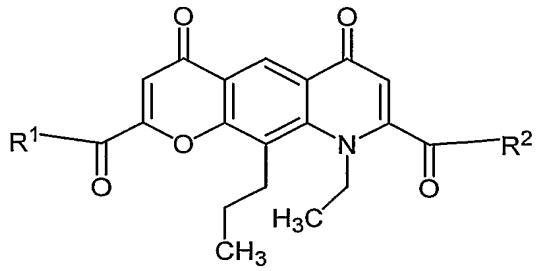
B^3 is an iNOS inhibitor having a carboxylic acid substituent; and

R is hydrogen or methyl.

3. A compound of formula I or II



I



II

wherein

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -O$^-$ X$^+$, wherein X$^+$ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

-O(C=O)R^4 is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of inducible nitric oxide synthase (iNOS);

-(C=O)R^4 is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is an inhibitor of iNOS;

R^5 is -O-R^{20}-U, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

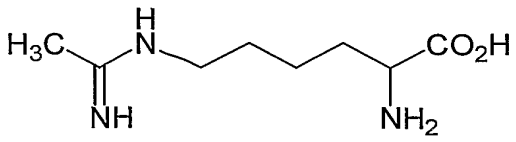
-NHR^6 is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is an inhibitor of iNOS;

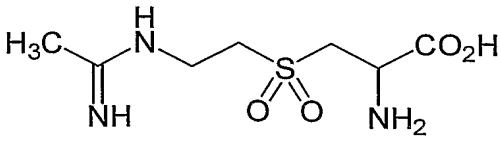
-OR^7 is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is an inhibitor of iNOS;

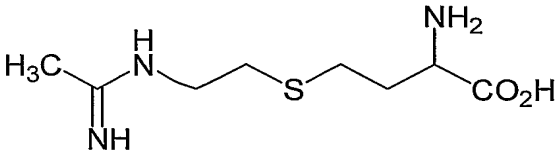
G is a linking moiety cleavable under physiologic conditions; and

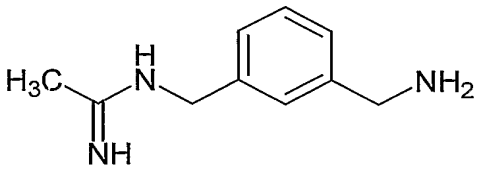
at least one of R^1, R^2 and R^3 must be -G-O(C=O)R^4, -NHR^6, -OR^7, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 or -(C=O)OR^7.

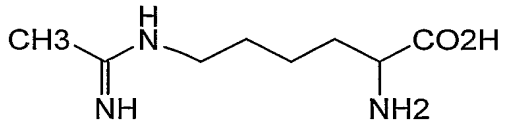
4. A compound according to claim 3 wherein R^4COOH and R^6NH_2 are chosen from:

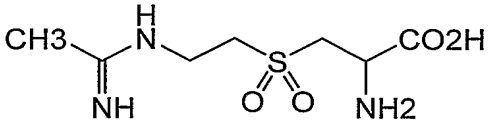


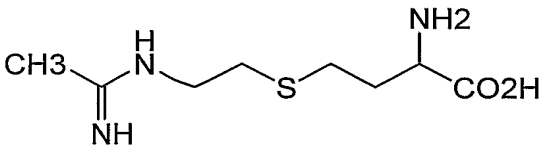


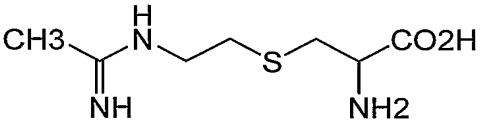


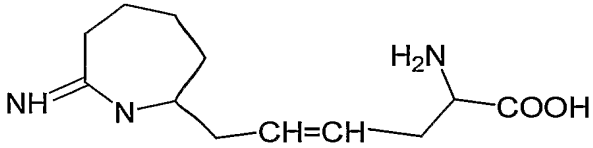


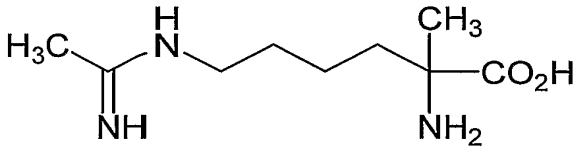


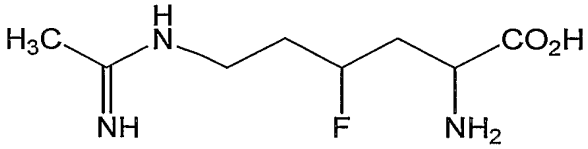


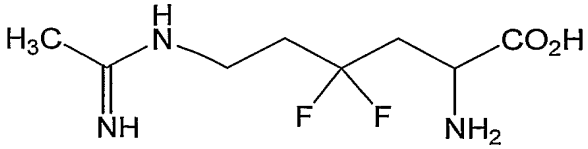


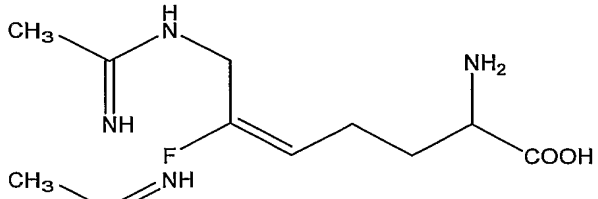


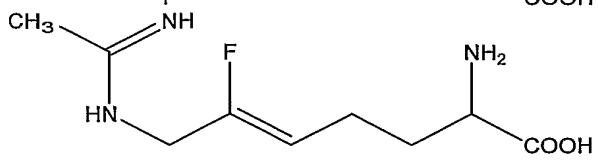


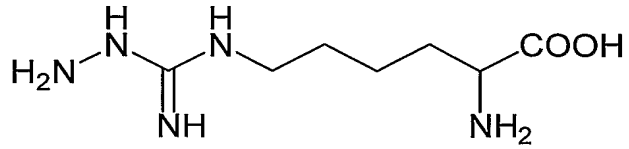






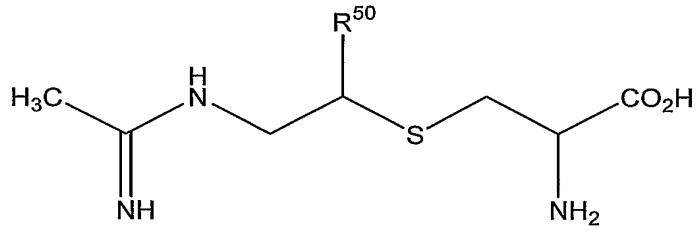






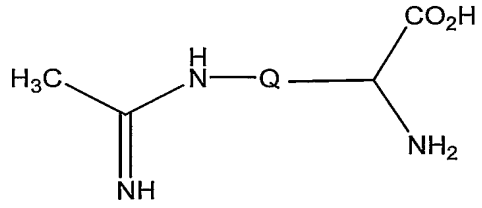
and .

5. A compound according to claim 3 wherein R^4COOH and R^6NH_2 are chosen from compounds of structure:



wherein R^{50} is chosen from C_1 to C_4 alkyl, C_3 to C_4 cycloalkyl, C_1 to C_4 hydroxyalkyl and C_1 to C_4 haloalkyl.

6. A compound according to claim 3 wherein R^4COOH and R^6NH_2 are chosen from compounds of structure:



wherein Q is chosen from $-CH_2CH=CHCH_2-$, $-(CH_2)_pX(CH_2)_q-$, -O- , $-NR^{51}-$ and $-(CH_2)_rA(CH_2)_s-$;

p is 2 or 3;

q is 1 or 2;

X is $S(O)_x$;

x is 0, 1 or 2;

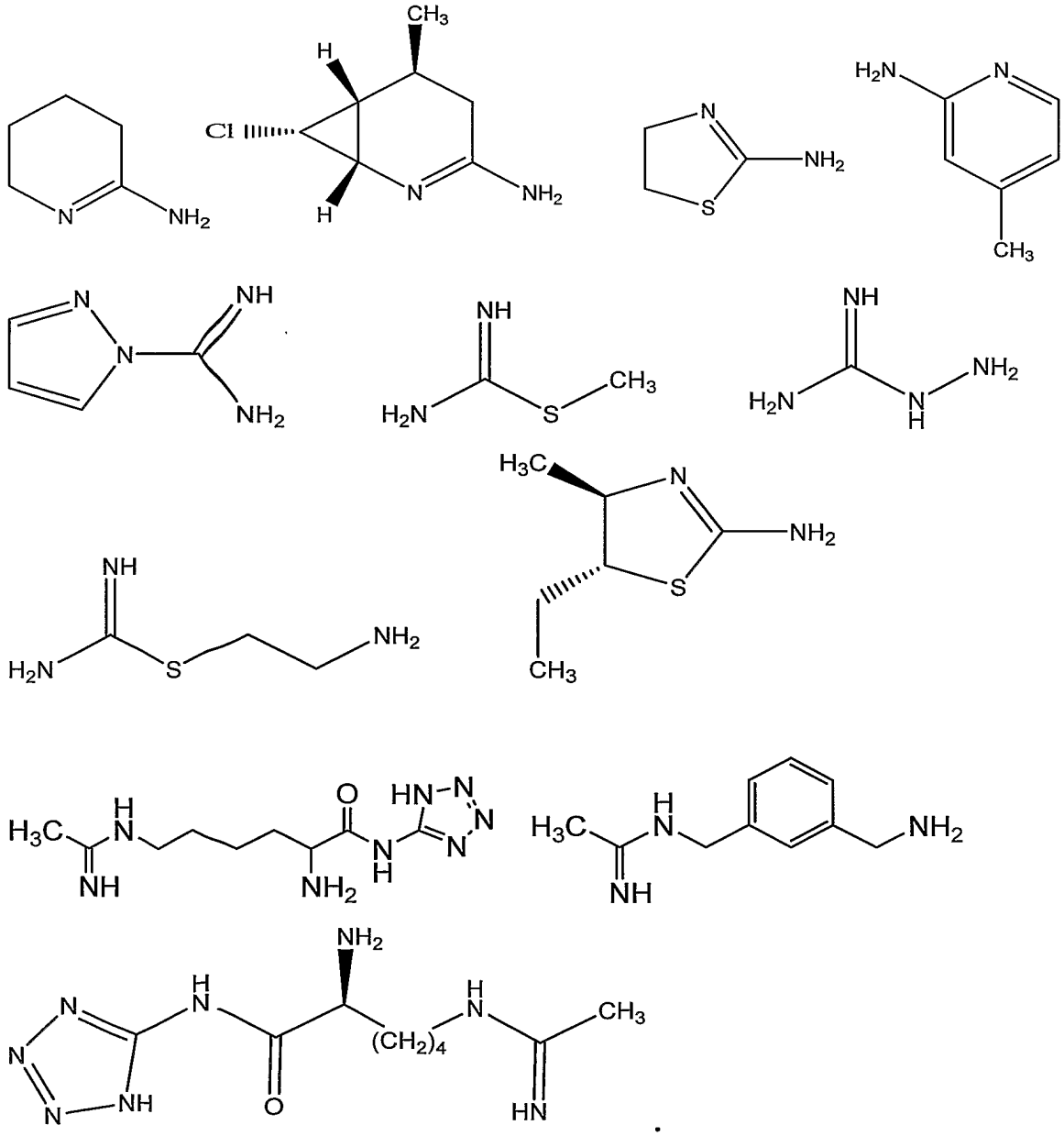
R^{51} is H or C_{1-6} alkyl;

r is 1 or 2;

s is 1 or 2; and

A is cyclobutyl, phenyl or pyridyl.

7. A compound according to claim 3 wherein R^6NH_2 is chosen from compounds of structure:



8. A compound according to claim 3 wherein

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, $-R^5$, $-NHR^6$, $-OR^7$ and $-O^- X^+$; and

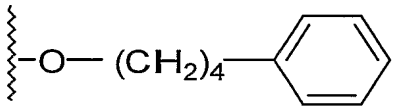
R^3 is chosen from hydrogen, $-(C=O)R^4$, $-(C=O)R^5$, $-(C=O)NHR^6$ and $-(C=O)OR^7$.

9. A compound according to claim 3 wherein at least one of

R^1, R^2 and R^3 is $-G-O(C=O)R^4$ or $-(C=O)-G-O(C=O)R^4$; and

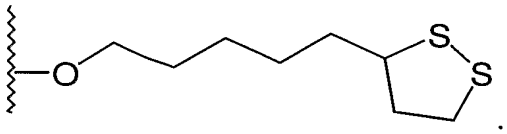
G is chosen from $-OCH_2-$ and $-OCH(CH_3)-$.

10. A compound according to any of claims 3-9 wherein R^5 is



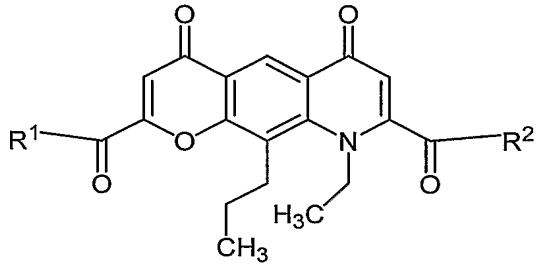
.

11. A compound according to any of claims 3-9 wherein R^5 is



.

12. A compound of formula II according to claim 3:



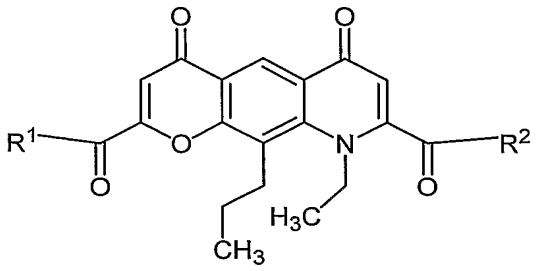
II

wherein

R^1 is chosen from hydroxy, R^5 and $-O^- X$;

R^2 is chosen from $-G-O(C=O)R^4$, $-NHR^6$ and OR^7 .

13. A compound of formula II according to claim 3:



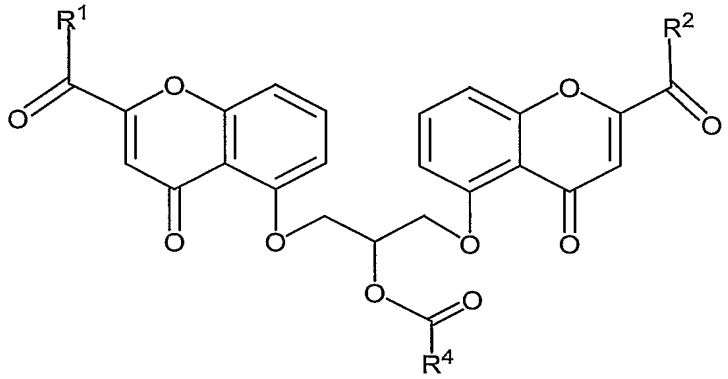
II

wherein

R^1 is chosen from -G-O(C=O)R^4, -NHR^6 and OR^7 ; and

R^2 is chosen from hydroxy, R^5 and $-O^- X$.

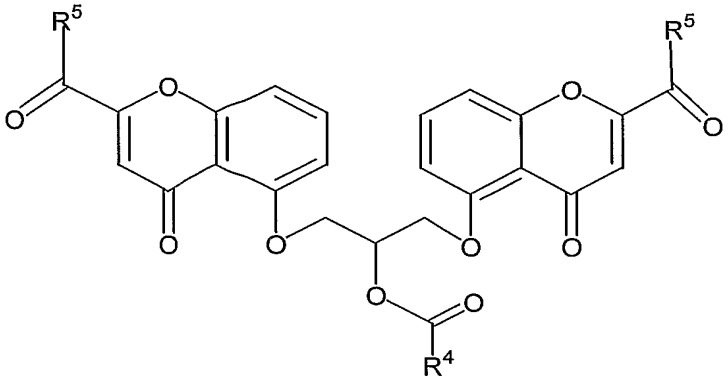
14. A compound according to claim 3 of formula



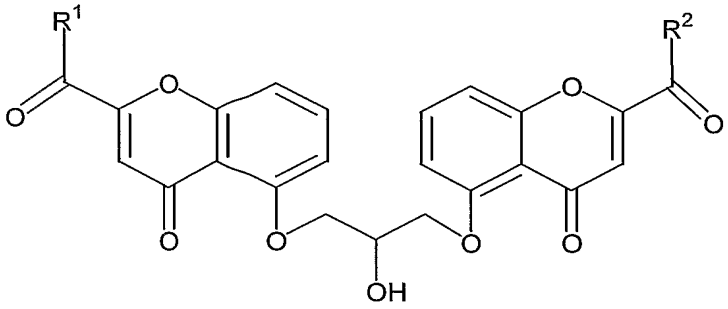
wherein

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy and $-O^- X^+$.

15. A compound according to claim 3 of formula:



16. A compound according to claim 3 of formula:

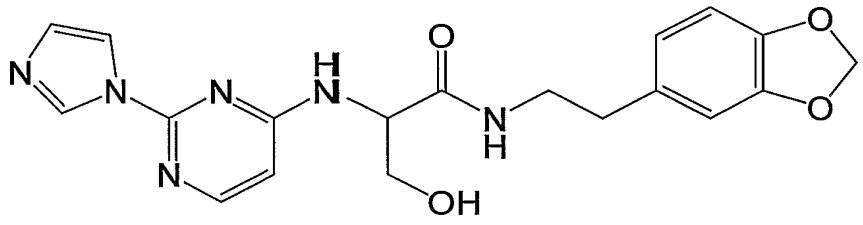


wherein

R^1 is chosen from -G-O(C=O)R^4, -NHR^6 and OR^7 ; and

R^2 is chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, R^5 and $-O^-X$.

17. A compound according to claim 3 wherein R^7 is



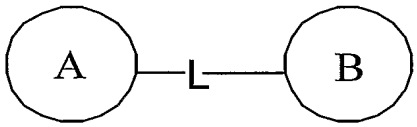
18. A pharmaceutical composition comprising a pharmaceutically acceptable carrier and a compound according to any of claims 1-9 and 12-17.

19. An aerosol pharmaceutical composition according to claim 18.

20. An oral pharmaceutical composition according to claim 18.

21. An oral pharmaceutical composition according to claim 20 in the form of a tablet, capsule or syrup.

22. A method for treating a pulmonary disorder comprising administering a compound represented by the structure:



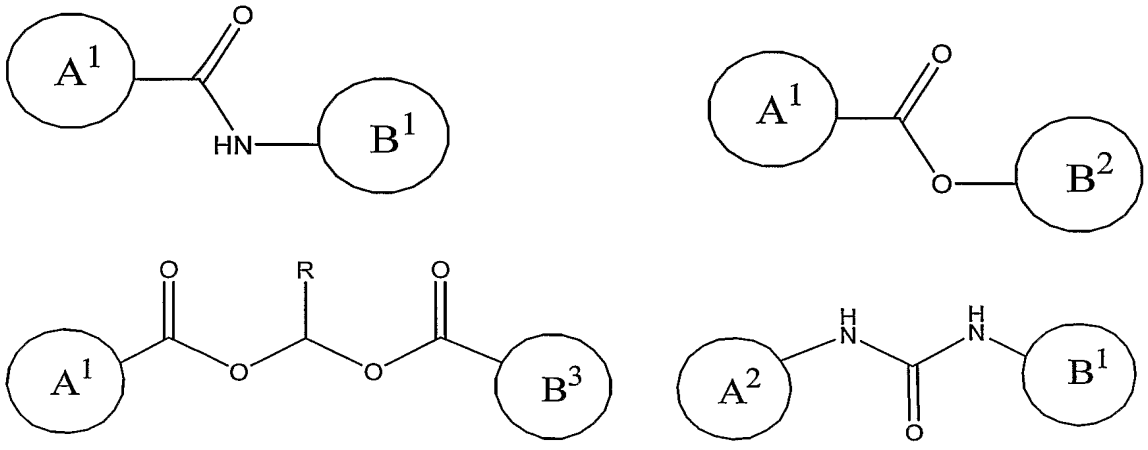
wherein

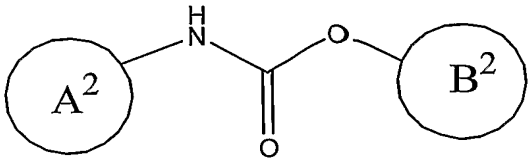
A is a mast-cell stabilizer;

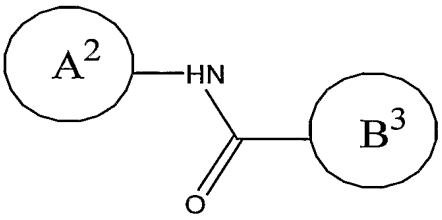
L is a covalent linkage;

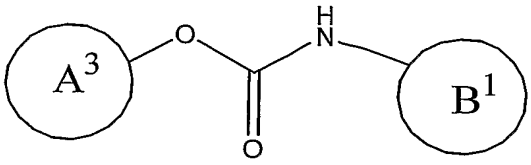
B is an iNOS inhibitor.

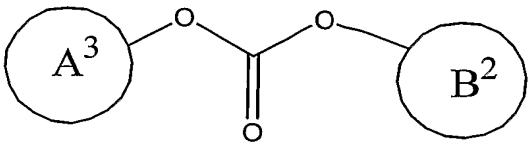
23. A method according to claim 22 for treating a pulmonary disorder wherein L is chosen from -CONH-, -COO-, -O(C=O)O-, -O(C=O)NH-, -NHCONH- and -(C=O)OCH(R)O(C=O)- and the compound is represented by a structure chosen from:

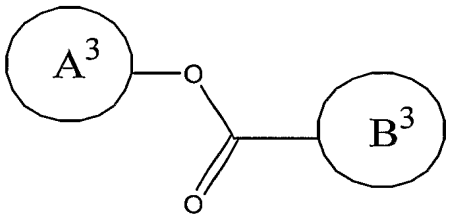












and

wherein

A^1 is a mast-cell stabilizer having a carboxylic acid substituent;

A^2 is a mast-cell stabilizer having an amine substituent;

A^3 is a mast-cell stabilizer having an alcohol substituent;

B^1 is an iNOS inhibitor having an amine substituent;

B^2 is an iNOS inhibitor having an alcohol substituent;

B^3 is an iNOS inhibitor having a carboxylic acid substituent; and

R is hydrogen or methyl.

24. A method for treating a pulmonary disorder comprising administering a compound according to any of claims 3-9 and 12-17.

25. A method according to claim 24 for treating bronchospasm.

26. A method according to claim 24 for inducing bronchodilation.

27. A method according to claim 24 for treating chronic obstructive pulmonary disease.

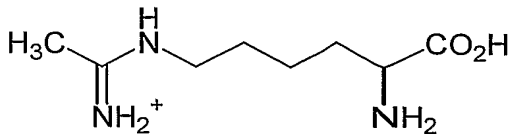
28. A method according to claim 24 for treating asthma.

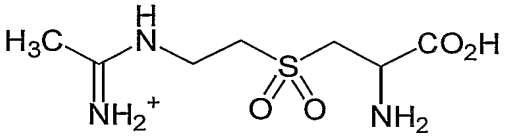
29. A method according to claim 24 for treating rhinitis.

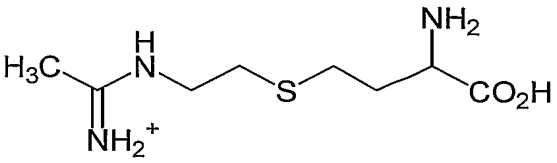
30. A method according to claim 24 wherein the pulmonary disorder is acute pulmonary vasoconstriction, pneumonia, traumatic injury, aspiration or inhalation injury, fat embolism in the lung, acidosis, inflammation of the lung, adult respiratory distress syndrome, acute pulmonary edema, acute mountain sickness, post cardiac surgery, acute pulmonary hypertension, persistent pulmonary hypertension of the newborn, perinatal aspiration syndrome, hyaline membrane disease, acute pulmonary thromboembolism, heparin-protamine reactions, sepsis, hypoxia, chronic pulmonary hypertension, bronchopulmonary dysplasia, chronic pulmonary thromboembolism, idiopathic pulmonary hypertension, primary pulmonary hypertension or chronic hypoxia.

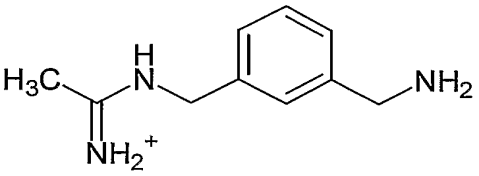
31. A method for treating a pulmonary disorder comprising co-administering a mast-cell stabilizer and an iNOS inhibitor in the form of a salt, in which one of said mast-cell stabilizer and said iNOS inhibitor is a cation or dication, and the other of said mast-cell stabilizer and said iNOS inhibitor is an anion or dianion.

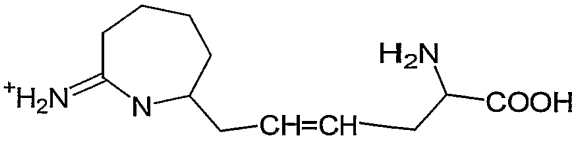
32. A method according to claim 31 wherein said cation is chosen from:

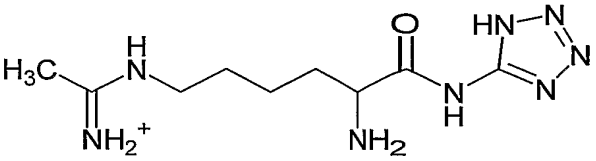


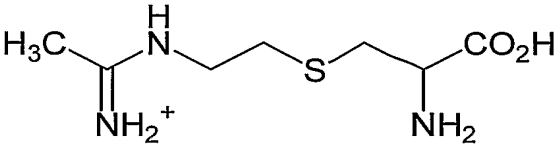


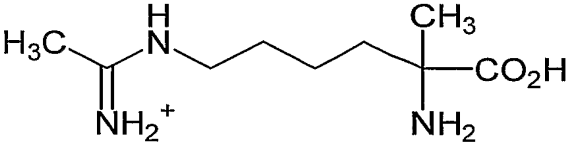


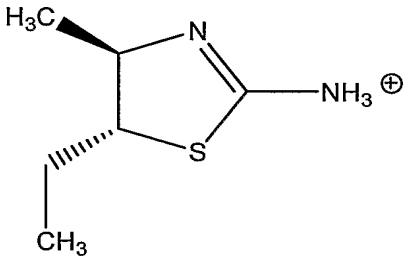




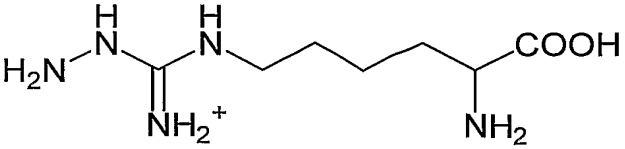


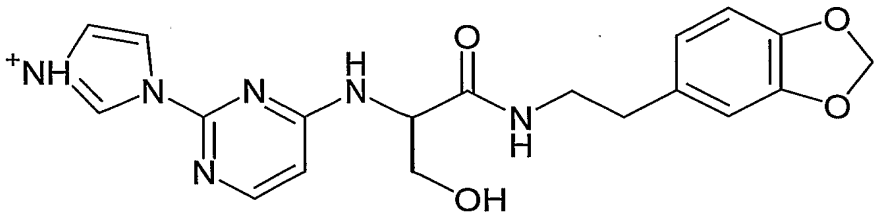


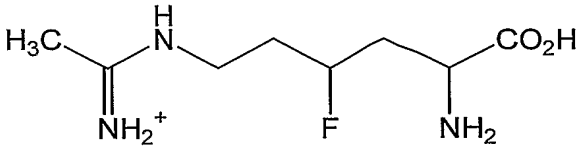


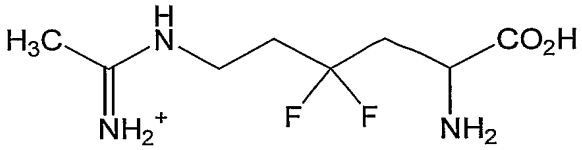


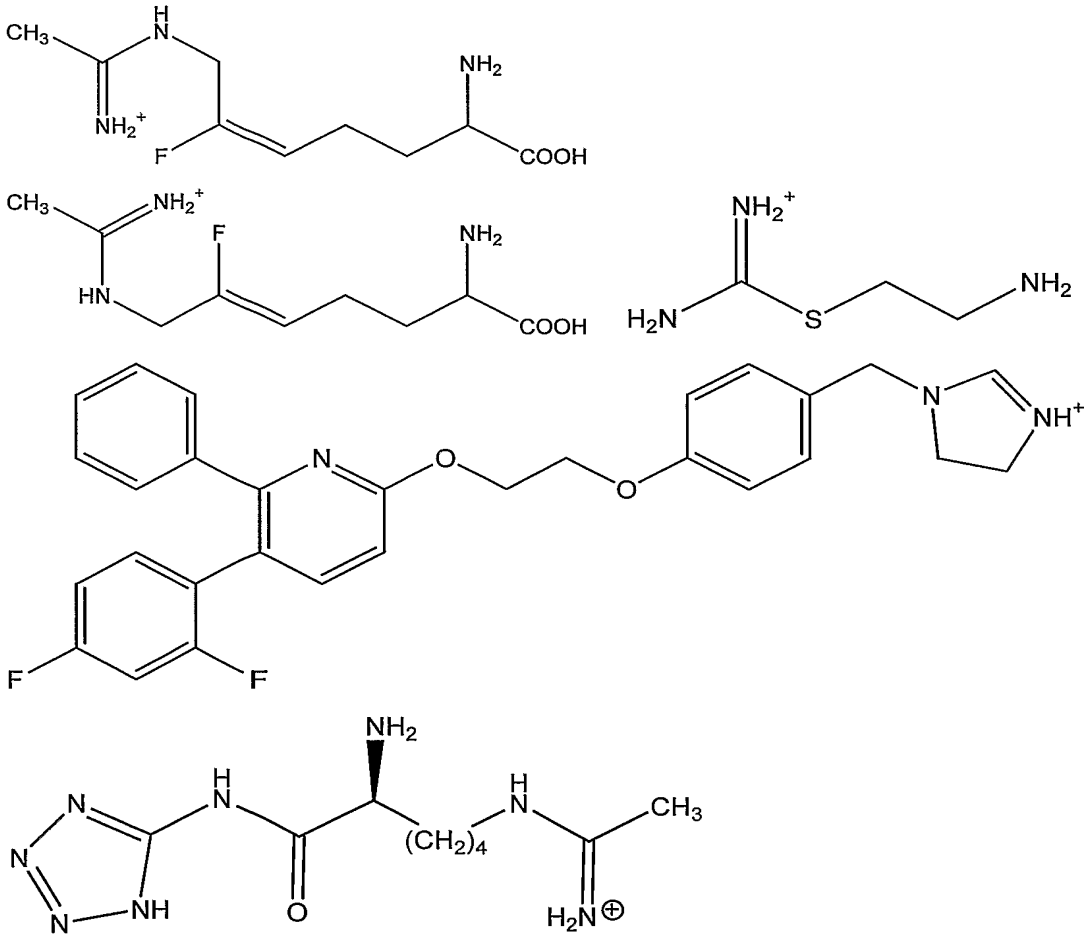
,





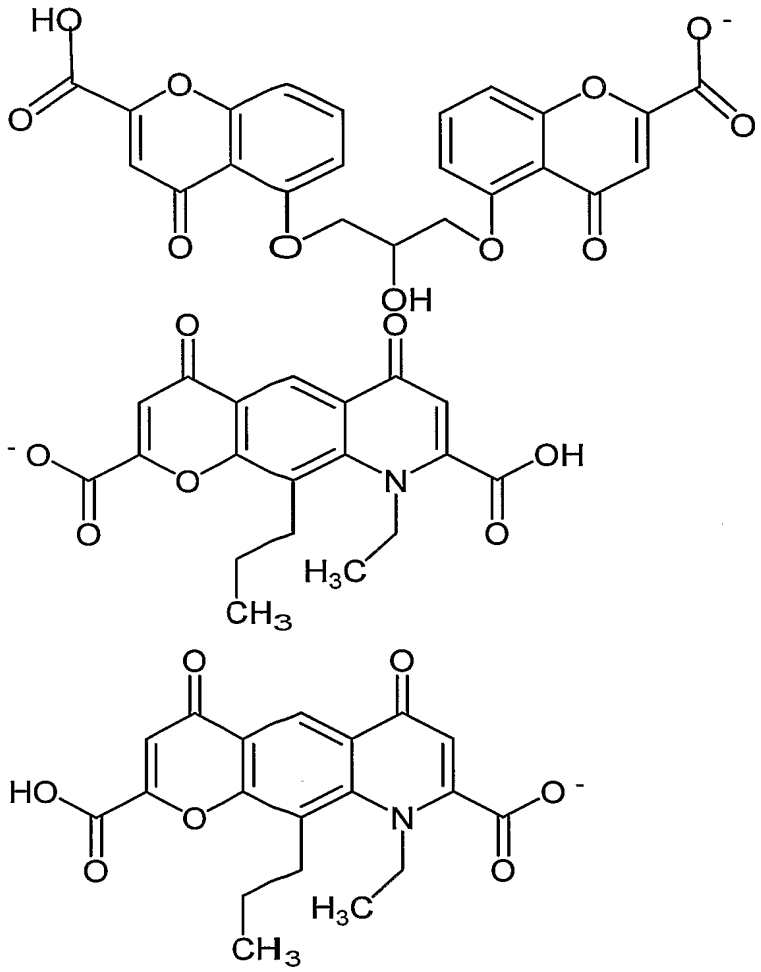






and their corresponding dications;

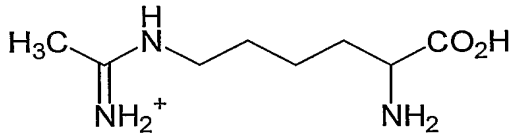
and said anion is chosen from:

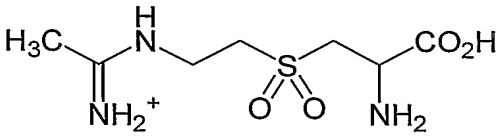


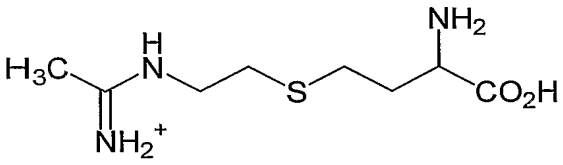
and their corresponding dianions.

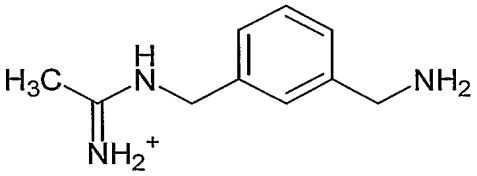
33. A salt comprising a mast-cell stabilizer and an iNOS inhibitor wherein one of said mast-cell stabilizer and said iNOS inhibitor is a cation or dication, and the other of said mast-cell stabilizer and said iNOS inhibitor is an anion or dianion.

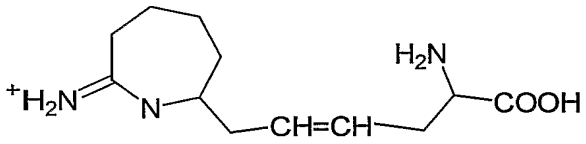
34. A salt according to claim 33 wherein said cation is chosen from:

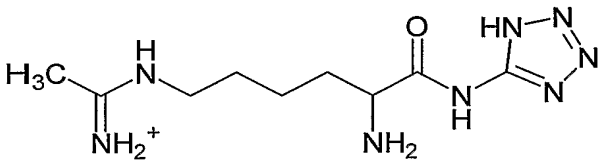


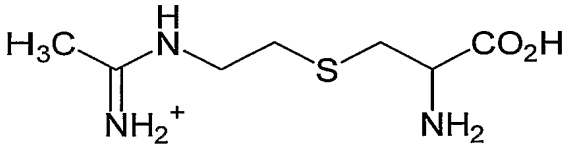


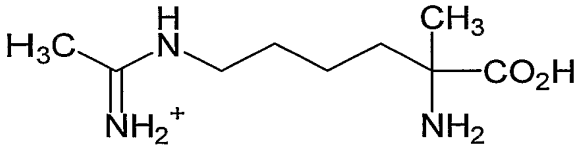


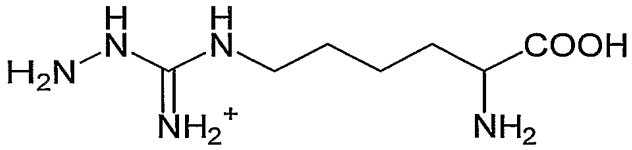


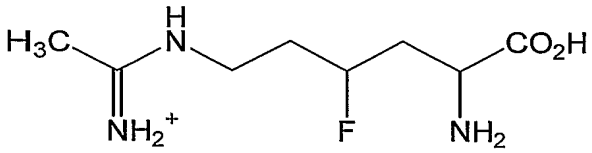


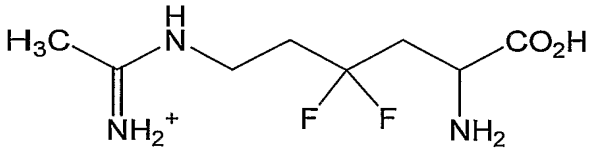


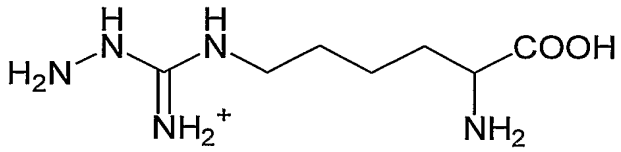


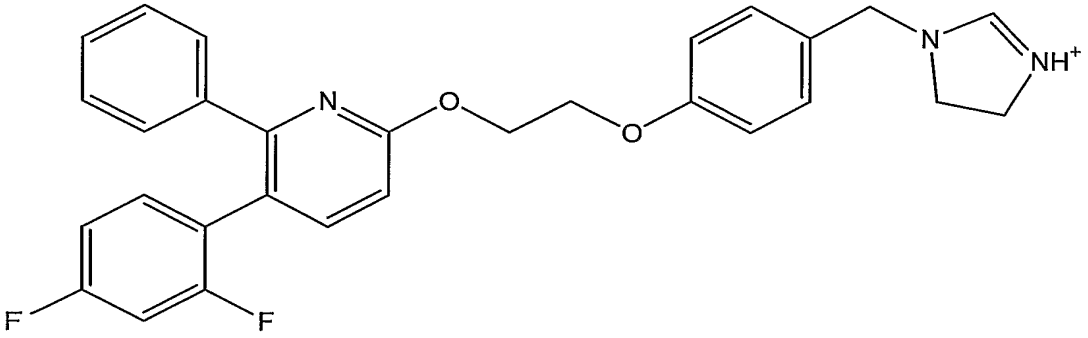


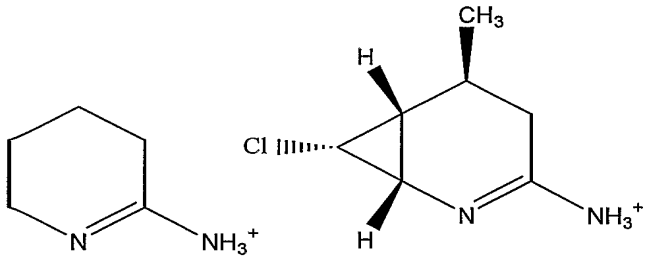


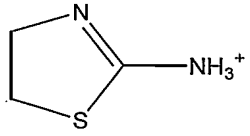


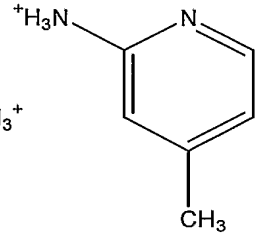


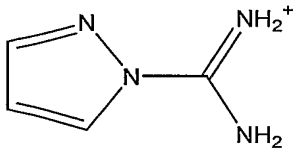


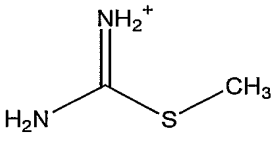


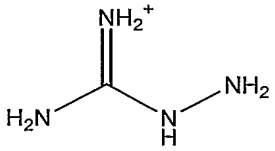


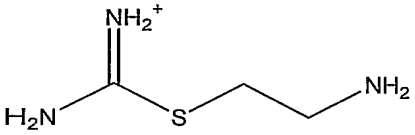


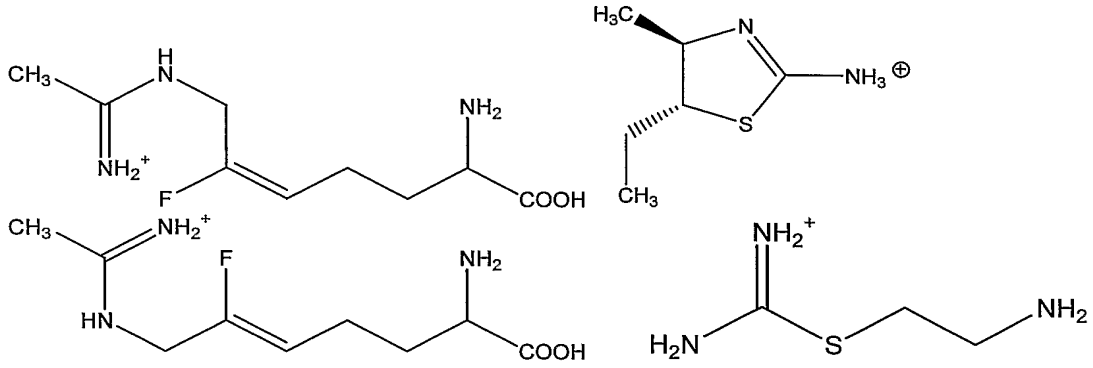




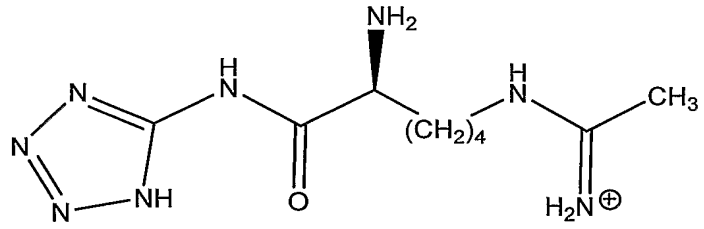






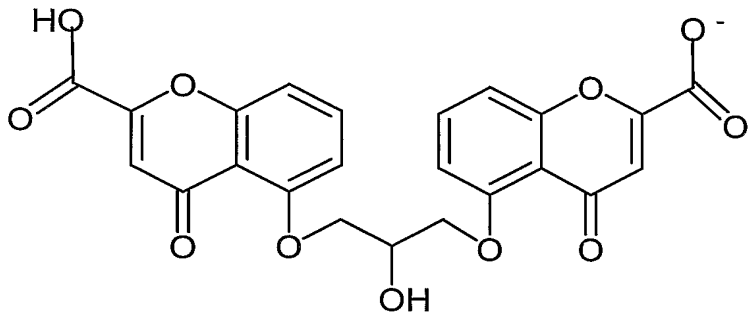


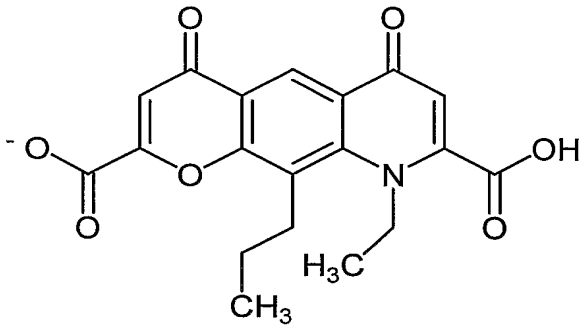
and

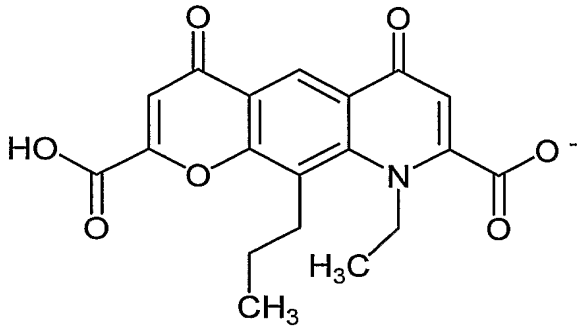


and their corresponding dications;

and said anion is chosen from:

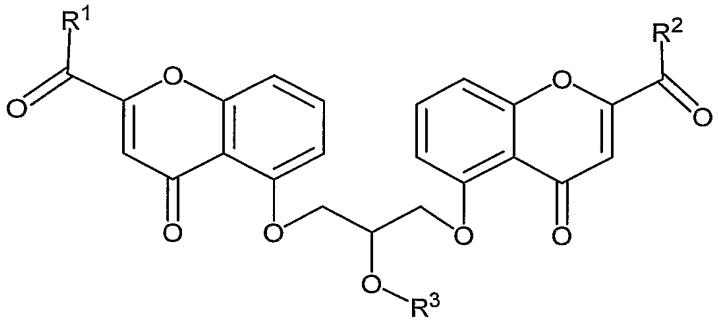




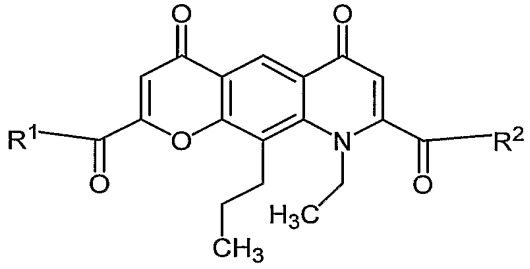


and their corresponding dianions.

35. A compound of formula I or II



I



II

wherein

R^1 and R^2 are chosen from hydroxy, C_1, C_2, C_3, C_4, C_5, and C_6 straight and branched alkoxy, -G-O(C=O)R^4, R^5, -NHR^6, -OR^7 and -O^- X^+, wherein X^+ is a pharmaceutically acceptable cation;

R^3 is chosen from hydrogen, -(C=O)R^4, -(C=O)-G-O(C=O)R^4, -(C=O)R^5, -(C=O)NHR^6 and -(C=O)OR^7;

$-O(C=O)R^4$ is the deshydrogen residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting inducible nitric oxide synthase (iNOS);

$-(C=O)R^4$ is the deshydroxy residue of a carboxylic acid, the parent of which, R^4COOH, is a chemical means for inhibiting iNOS;

R^5 is $-O-R^{20}-U$, wherein U is chosen from hydrogen, (1,2-dithiolan-3-yl) and phenyl, and R^{20} is a divalent C_1 to C_{20} alkane or oxaalkane residue;

$-NHR^6$ is the deshydrogen residue of an amine, the parent of which, R^6NH_2, is a chemical means for inhibiting iNOS;

$-OR^7$ is the deshydrogen residue of an alcohol, the parent of which, R^7OH, is a chemical means for inhibiting iNOS;

G is a linking moiety cleavable under physiologic conditions; and

at least one of R^1, R^2 and R^3 must be $-G-O(C=O)R^4$, $-NHR^6$, $-OR^7$, $-(C=O)R^4$, $-(C=O)-G-O(C=O)R^4$, $-(C=O)R^5$, $-(C=O)NHR^6$ or $-(C=O)OR^7$.